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REVIEW

Neurologic complications after liver transplantation

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Abstract

Neurologic complications are relatively common after solid organ transplantation and affect 15%-30% of liver transplant recipients. Etiology is often related to immunosuppressant neurotoxicity and opportunistic infections. Most common complications include seizures and encephalopathy, and occurrence of central pontine myelinolysis is relatively specific for liver transplant recipients. Delayed allograft function may precipitate hepatic encephalopathy and neurotoxicity of calcineurin inhibitors typically manifests with tremor, headaches and encephalopathy. Reduction of neurotoxic immunosuppressants or conversion to an alternative medication usually result in clinical improvement. Standard preventive and diagnostic protocols have helped to reduce the prevalence of opportunistic central nervous system (CNS) infections, but viral and fungal CNS infections still affect 1% of liver transplant recipients, and the morbidity and mortality in the affected patients remain fairly high. Critical illness myopathy may also affect up to 7% of liver transplant recipients. Liver insufficiency is also associated with various neurologic disorders which may improve or resolve after successful liver transplantation. Accurate diagnosis and timely intervention are essential to improve outcomes, while advances in clinical management and extended post-transplant survival are increasingly shifting the focus to chronic post-transplant complications which are often encountered in a community hospital and an outpatient setting.

Key words: Liver transplantation; Neurologic complications; Meningoencephalitis; Seizures; Stroke; Critical illness myopathy

Core tip: Neurologic complications after liver transplantation are still a major source of morbidity and mortality and careful approach to possible immunosuppressant neurotoxicity and opportunistic infections is needed. Most common neurologic complications include encephalopathy, seizures and cerebrovascular complications, but opportunistic central nervous system infections and central pontine myelinolysis may be associated with significant morbidity as well. Accurate diagnosis and timely intervention are essential to improve outcomes, while advances in clinical management of neurologic post-transplant complications and extended post-transplant survival are increasingly shifting the focus to chronic post-transplant complications which are often encountered in a community hospital and an outpatient setting.

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INTRODUCTION

There have been more than 6000 liver transplantations performed in United States in 2011, including living donor and cadaveric allografts. Since the first successful liver transplantation by Dr Starzl in 1963, there has been tremendous and dynamic progress of surgical and postoperative protocols leading to 1-year and 5-year post-

transplant survival rates at 88% and 74%, respectively[1]. Successful liver transplantation is also associated with improved quality of life for allograft recipients[2]. However, a variety of post-transplant complications, which may not be directly related to allograft function, complicate recovery of transplant recipients. Neurologic complications are still fairly common after solid organ transplantation and affect 30%-60% of allograft recipients[3], including 15%-30% of liver allograft recipients (Table 1)[4-8]. More recent studies demonstrate decreasing frequency of neurologic complications reflecting improved transplant outcomes and advanced management regimens. Improved survival of transplant recipients has also somewhat shifted the spectrum of neurologic complications from acute post-transplant inpatient emergencies towards chronic outpatient complications, although severe post-transplant complications may occur at any given time. Decreased frequency of neurologic complications was also reported for patients receiving living donor allografts when compared to cadaveric allografts (20% *vs* 27%), but there is a donor-related morbidity and living-liver donors may rarely suffer neurologic complications as well[7]. Major neurologic complications include alterations of consciousness, seizures, cerebrovascular complications and central nervous system (CNS) infections, similarly as with other solid organ transplants, and also central pontine myelinolysis (CPM) which is characteristic for liver transplantation. Pre-transplant liver failure may be associated with various neurologic complications directly related to liver dysfunction (*e.g.*, hepatic encephalopathy), or related to systemic disorders associated with major neurologic manifestations (*e.g.*, Wilson's disease) (Table 2). Stabilization of liver function following successful transplantation may subsequently lead to improvement of neurologic symptoms as well. During the post-transplant clinical course, the surgical procedure of transplantation, chronic immunosuppression and various toxic-metabolic disorders may precipitate a wide spectrum of neurologic complications[4-7,9]. Premorbid and new onset psychiatric and behavioral disorders may also negatively affect compliance with immunosuppression regimens and complicate post-transplant management[10]. Neurologic post-transplant complications can develop at any given time after transplantation and often multiple risk factors are present. The outcome of transplantation is usually not affected by neurologic complications but additional morbidity may delay post-transplant recovery[11]. Additionally, opportunistic infections and immunosuppressant neurotoxicity may complicate management of immunosuppressive medications and effective prevention of allograft rejection.

Overall, post-transplant neurologic morbidity in liver allograft recipients is often related to opportunistic infections and immunosuppressant neurotoxicity, but most patients will have multiple risk factors for development of neurologic complications (Table 3).

NEUROTOXICITY OF IMMUNOSUPPRESSIVE MEDICATIONS

Long-term immunosuppression increases the risk of opportunistic infections, but immunosuppressive medications can also exhibit direct neurotoxicity[12-15]. Maintenance immunosuppressive regimens typically include a combination of inhibitors of calcineurin or mTOR, antimetabolites and corticosteroids, while induction and rejection treatments may also include polyclonal and monoclonal antibodies[12,16].

Calcineurin inhibitors (CNI), cyclosporine and tacrolimus, are one of mainstays of immunosuppression after organ transplantation. However their use may be associated with various neurologic complications. In the early posttransplant period, there is a greater risk of CNI neurotoxicity due to higher doses, intravenous use and impaired blood-brain barrier. Clinical manifestations of CNI toxicity are usually accompanied by elevated levels of tacrolimus or cyclosporine, but symptoms may present even with normal serum levels. Hypomagnesemia and hypocholesterolemia may also increase the risk of CNI toxicity[14]. Neurotoxicity of CNI typically manifests with tremor, headache, and encephalopathy[12-15]. Presence of altered consciousness and cortical blindness may indicate posterior reversible encephalopathy syndrome (PRES) with characteristic imaging findings on MRI of the brain with an increased T2-signal posteriorly in white matter[17-19]. PRES is associated with reversible vasogenic subcortical edema and may accompany various medical conditions and drug neurotoxicity[17]. In transplant recipients, PRES is most commonly reported with cyclosporine or tacrolimus neurotoxicity, but there are also rare reports of PRES with sirolimus[20]. There is no specific therapy for CNI neurotoxicity other than symptomatic treatment (*e.g.*, antiepileptics for seizure management), and with dose reduction or switching to alternative immunosuppressives[3,14,21].

Recently introduced mTor inhibitors, sirolimus and everolimus, are usually better tolerated than CNI, but rare case of sirolimus-induced PRES was reported as well[20,22].

Toxicity of other immunosuppressive medications may also precipitate various neurologic symptoms. Corticosteroids may increase the risk of critical illness myopathy, or precipitate steroid myopathy, mood disorders or psychosis. Other common side-effects of corticosteroids include weight gain, osteoporosis and hyperglycemia. Rarely, corticosteroid use may lead to epidural lipomatosis which may manifest with radiculopathies or compressive myelopathy[23]. Mycophenolate is usually well tolerated, but some patients may complain of headaches.

OPPORTUNISTIC INFECTIONS

Chronic immunosuppression increases the risk of opportunistic infection as a result of imbalance between immune status and exposure to infectious agents[24,25].

Table 1 Neurologic complications of liver transplantation

Ref.	*n*	Total	Seizure	Stroke	Brain hemorrhage	Encephalopathy	CNS infection
Bronster *et al*[4]	463	20%	8.20%	0.60%	1.50%	11.8	1.2
Lewis *et al*[6]	657	27%	6	4%[1]	-[1]	11.0	1.1
Saner *et al*[7]	174	25%	2.8	0.60%	1.20%	17.8	0.0
Kim *et al*[5]	319	15%	1.60%	0.30%	0.60%	2.0	0.3
Vizzini *et al*[8]	395	16%	1%	1.30%	2.5	5.3	0.0

[1]Combined ischemic strokes and brain hemorrhage. CNS: Central nervous system.

Table 2 Liver failure and associated neurologic complications

Underlying condition	Neurologic complication
Hepatic failure	Encephalopathy, acquired hepatocerebral degeneration, parkinsonism, neuropathy, myelopathy, asterixis
Wilson's disease	Psychiatric complications, dystonia, parkinsonism
Primary biliary cirrhosis	Neuropathy, dysautonomia
Familial amyloidosis (transthyretin)	Neuropathy, dysautonomia

Table 3 Risk factors for neurologic complications after liver transplantation

Underlying condition	Neurologic complication
Chronic hyponatremia	Central pontine and extrapontine myelinolysis
High levels of immunosuppression	Immunosuppressant neurotoxicity, opportunistic infections
Endemic and nosocomial exposures	Opportunistic infections
Sepsis	CIM/CIP, septic encephalopathy
Multiple organ failure	CIM/CIP
Hepatic dysfunction	Encephalopathy
History of alcohol abuse	Encephalopathy

Modified from Linden *et al*[11]. CIM/CIP: Critical illness myopathy/polyneuropathy.

Early signs of infection in immunosuppressed patients may be masked by medications or other medical problems, including allograft rejection. Exposure to infectious agents may stem from donor-related infections, recipient-related infections, nosocomial infections and community infections. Rate of opportunistic infections has declined due to improved surveillance measures and prophylaxis. Most common causes of opportunistic CNS infections in immunosuppressed transplant recipients are fungi and viruses, while bacterial and protozoic infections are less common[24,25]. During initial post-transplant period (first 30 d), acquired infections are often related to pre-transplant colonization or surgical procedures, and there are also rare donor-to-recipient transmissions *via* allograft[26,27]. The risk of acquired opportunistic infections increases at 1 mo following the transplantation[25]. At 6 mo after transplantation, the risk of infections gradually diminishes as immunosuppressants are often tapered down. However, the risk does persist long-term and this may further rise with rejection episodes requiring more aggressive immunotherapy. Endemic exposure and travel may result in unusual causative agents including Naegleria, Leishmania, Coccidioides or Histoplasma[28]. Prevalence of CNS infections in transplant patients has been previously estimated at 5%, but most recent series demonstrate much less frequent infections with better immunosuppressive and preventive strategies[3,8]. However, potential signs of CNS infections are always to be taken seriously in transplant recipients, and due to immunosuppression and complex metabolic disturbances, the initial onset of symptoms may be obscured in some patients.

Clinically, opportunistic CNS infections may present with signs of meningitis or meningoencephalitis, or with more focal findings suggestive of an abscess (fungi, bacteria). Viral infections may also present with focal signs due to preferential involvement of some brain regions [*e.g.*, limbic encephalitis with Human herpesvirus (HHV)-6 infection][29]. New onset of severe back pain may suggest spinal epidural abscess, requiring prompt intervention[30].

Viral infections are often caused by Cytomegalovirus (CMV), herpes simplex virus, varicella zoster virus (VZV), Epstein-Barr virus (EBV) or HHV-6. CMV infections are fairly common in transplant recipients, but CNS involvement is rare. Dermatomal zoster may precede CNS infection caused by VZV. Infrequently, EBV infection may precipitate posttransplant lymphoproliferative disorder with CNS involvement[31]. Treatment of post-transplant lymphoproliferative disease may include irradiation, chemotherapy or biological (rituximab), and immunosuppression is often reduced as well. Reactivation of HHV-6 infection after liver transplantation is typically asymptomatic, but rarely it may lead to limbic encephalitis and post-encephalitic epilepsy[32]. Progressive multifocal leukoencephalopathy (PML) is an uncommon fatal brain disorder caused by JC virus, and its imaging features may resemble PRES[19]. However, PML does not improve with reduction of CNI dosing and typically follows a progressive course. It does not usually respond to antiviral treatment or reduction of immunosuppression, and is typically associated with gradual progression over several months[33].

Most common fungal CNS infections are caused by Cryptococcus neoformans and Aspergillus species[24,34], while opportunistic bacterial CNS infections are less common after liver transplantation. Fungal CNS infections are usually associated with systemic fungal infections, and may also extend locally following fungal sinusitis[34]. Increased risk of CNS aspergillosis has been reported after liver retransplantation[35]. Treatment of

fungal CNS infections in immunocompromised patients is often limited by delayed diagnosis and drug toxicity (nephrotoxicity with Amphotericin), so morbidity and mortality still remain high. Clinical presentations include meningitis, brain hemorrhage or abscesses. Vasoinvasive CNS fungal infections (*e.g.*, Aspergillus species) are often associated with hemorrhagic strokes[36]. Fungal brain abscesses may also manifest with seizures or focal neurologic signs. Candida is the most common fungal infection after liver transplantation, but CNS infections caused by Candida species are rare.

Bacterial CNS infections are relatively rare after liver transplantation, but the risk may be increased with environmental exposure. Exposure to contaminated dairy may lead to CNS listeriosis which may present with rhombencephalitis and usually responds to treatment, especially with early diagnosis[37]. Nocardia species are ubiquitous saprophytes and are unlikely to infect non-immunocompromised individuals. Clinical manifestations range from pulmonary infection to abscesses and CNS infection[38]. Timely diagnosis usually leads to an effective treatment, although surgical drainage may be needed for cerebral abscesses.

Toxoplasmosis is the most common protozoal infection in transplant recipients and other immunocompromised individuals. Toxoplasmosis has been reported in up to 0.18% of solid organ transplant recipients and may be associated with exposure to cats. Seronegative transplant recipients are at 15-fold greater risk of toxoplasmosis and should be treated prophylactically with trimethoprim-sulfametoxazole or pyrimethamine[39]. Freshwater swimming may lead to amebic encephalitis which carries almost 100% mortality[40].

Despite improved prevention and therapeutic advances, opportunistic CNS infections still carry severe morbidity and high mortality. Therefore, prompt and accurate diagnosis and early institution of therapy of CNS infections are essential for improvement of outcomes.

HEPATIC ENCEPHALOPATHY

Chronic pretransplant hepatic encephalopathy increases the risk of posttransplant neurologic complications[41], but the improving graft function may gradually lead to significant cognitive improvement. Delayed allograft function can precipitate hepatic encephalopathy and affect pharmacokinetics of different hepatically-metabolized medications. Clinical manifestations of hepatic encephalopathy range from subtle cognitive slowing and memory difficulties, to somnolence, stupor and coma[42]. Patients often exhibit asterixis and parkinsonism. Pathophysiology of brain dysfunction associated with hepatic encephalopathy is not completely understood, but the role has been proposed for ammonia and manganese[43].

High ammonia level with improving graft function may also be related to acquired urea cycle enzyme abnormalities, and these may be difficult to treat[44].

POST-TRANSPLANT ENCEPHALOPATHY

Hepatic encephalopathy is a frequent complication of advanced liver diseases and it usually improves after successful liver transplantation. Failure to awaken after liver transplantation may be one of the first signs of abnormal graft function[45], and is always taken seriously. Primary graft failure may manifest with unresponsiveness, hepatorenal syndrome and severe coagulopathy, and carries high mortality.

Overall, common causes of post-transplant encephalopathy in liver allograft recipients include hepatic dysfunction, medication toxicity, infectious causes (CNS infections or septic encephalopathy), complex metabolic disturbances (uremia, CPM), cerebrovascular events or seizures[45]. Higher risk of encephalopathy was reported in patients with history of severe hepatic encephalopathy, ethanol-related hepatic failure, metabolic liver disease, greater severity of pre-transplant liver injury (defined by Child-Pugh or MELD scores) and non-elective liver transplantation[41,46,47]. Quite often, multiple co-existing risk factors will be identified in individual patients and careful clinical evaluation will be needed to determine the most appropriate course of action. In early post-transplant course, a delayed arousal can be related to persisting hepatic dysfunction, CNI neurotoxicity or intracranial hemorrhage. Higher doses and intravenous delivery increase the risk of CNI neurotoxicity. Neuroimaging studies may show evidence of PRES or intracerebral hemorrhage, while EEG might reveal triphasic waves suggestive of hepatic encephalopathy or nonconvulsive status epilepticus[19,48]. Chronic immunosuppression later increases the risk of opportunistic infections with direct CNS involvement, and lumbar puncture should be considered in patients with possible CNS infection Opportunistic CNS infection often present in the setting of systemic infection, but systemic infections may also precipitate septic encephalopathy in the absence of direct CNS involvement.

CPM

Relatively high prevalence of CPM or extrapontine myelinolysis (EPM) in the early period after liver transplantation is probably attributable to large fluid shifts, similarly as in rapid correction of hyponatremia (Table 2). Due to massive fluid shifts in early posttransplant period, the risk of CPM/EPM is also higher in first 48 h after transplantation. It has been estimated that up to 1%-2% of liver transplant recipients may develop CPM/EPM[5,6,49]. True prevalence of CPM remains uncertain as symptoms may be overshadowed by other complications and imaging changes may resolve over time[50]. Greater risk of CPM/EPM has been reported in patients with preoperative hyponatremia and worse liver dysfunction[49]. Clinical manifestations of CPM include stupor and spastic tetraparesis[51]. Neuroimaging studies typically show area of T2 hyperintensity on MRI imaging in central pons[19]. Supportive treatment of CPM is the standard of care,

and at this time there is no sufficient evidence to support other types of treatment for CPM, including plasma exchange or IVIG.

SEIZURES

Seizures after liver transplantation are often precipitated by CNI neurotoxicity, followed by CNS infections and cerebrovascular complications[52,53]. Complex metabolic and toxic disturbances may also precipitate nonconvulsive status epilepticus which may go unnoticed if EEG is not done. In patients with failure to awaken, EEG will also provide critical distinction between toxic metabolic encephalopathy and NCSE, although interpretation may present a unique challenge with multiple medical and technical factors to be considered[48]. Focal brain lesions after cerebrovascular complications, CNS infections, or even PRES, may precipitate symptomatic epilepsy requiring long-term maintenance therapy with antiepileptic medications. While acute treatment of status epilepticus after transplantation is usually the same as in non-transplant patients, long-term maintenance treatment of seizures has to take into account complex metabolic disturbances, altered pharmacokinetics and drug-drug interactions[54]. The presence of liver and kidney insufficiency will affect levels of antiepileptics, and we usually try to avoid potentially hepatotoxic medications after liver transplantation. Additionally, for long-term maintenance treatment of seizures after liver transplantation it is preferable to avoid medications which can affect CNI pharmacokinetics. Preferential choices include levetiracetam, gabapentin and lacosamide, but phenytoin is still often used due to availability and price[55].

CEREBROVASCULAR COMPLICATIONS

Cerebrovascular complications, including ischemic strokes and intracranial hemorrhage, are rare after liver transplantation and most studies report prevalence of 2%-4% in transplant recipients[4-7]. Higher risk of cerebrovascular complications has been reported in older recipients and with pretransplant diabetes, similarly as in general population[56].

Ischemic strokes are overall less common than intracranial hemorrhages, and are often associated with similar risk factors as in general population, including hypertension and hyperlipidemia. Sudden clinical deterioration may be related to intracranial bleeding, and vasoinvasive fungal CNS infections may manifest with hemorrhagic strokes. Increased risk of brain hemorrhage has been demonstrated in patients with thrombocytopenia and overwhelming infections[57]. That risk is further compounded by coagulopathy associated with hepatic failure. Hepatic encephalopathy is also associated with dysregulation of cerebral blood flow autoregulation[58].

Rarely, thrombotic microangiopathy resembling thrombotic thrombocytopenic purpura may develop leading to kidney failure and even brain ischemia. This may improve with a switch or reduction of CNI dosage and plasma exchange[59,60].

NEUROMUSCULAR COMPLICATIONS

Neuromuscular complications after liver transplantation are relatively uncommon, but post-transplant recovery may be complicated by critical illness myopathy in 7% of liver transplant recipients[61]. Perioperative neuropathies are also relatively rare and few patients may develop post-transplant demyelinating inflammatory polyneuropathy[62,63]. Uncommonly, an injury of the phrenic nerve during liver transplantation may result in hemidiaphragm paralysis, and trauma associated with venovenous bypass may lead to brachial plexus injury[64].

Alcohol-induced toxic neuropathy is relatively common in patients with alcoholic liver cirrhosis. Neuropathy related to alcohol toxicity may improve or even resolve after successful liver transplantation[65]. Neuropathy related to familial amyloidosis may improve after liver transplantation, although some symptoms usually persist (Table 2)[66].

Herpes zoster has been reported in 5.7% of liver transplant recipients with median onset of 9 mo after transplantation, and frequent occurrence of postherpetic neuralgia[67].

NEUROLOGIC COMPLICATIONS IN LIVE LIVER DONORS

Live-donor liver transplantation is a life-saving procedure, especially in the absence of appropriate cadaveric liver allografts. However, this is not an entirely benign procedure and it is associated with postoperative complications in about 16% of live donors and a donor mortality of 0.2%[68]. Rarely, live-donor liver transplantation may be also associated with donor neurologic complications, including brachial plexopathy[69].

NEUROLOGIC DISORDERS ASSOCIATED WITH LIVER FAILURE

Various liver diseases are often associated with neurologic complications including Wilson's disease, hepatitis C (with or without cryoglobulinemia), primary biliary cirrhosis, and alcoholic cirrhosis. Liver failure resulting from different causes may also manifest with various neurologic symptoms including hepatic encephalopathy, parkinsonism associated with hepatocerebral degeneration, asterixis, tremor and hepatic neuropathy[42,70-72]. Additionally, multisystemic disorders associated with liver failure (*e.g.*, familial amyloidosis) may also precipitate various neurologic complications which may improve or resolve after successful liver transplantation (Table 2)[65,72-74].

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